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ORANGES, Carlo M, *et al.* Hard palate melanoma: a population-based analysis of epidemiology and survival outcomes. *Anticancer Research*, 2018, vol. 38, no. 10, p. 5811-5817

PMID : 30275204

DOI : 10.21873/anticancer.12921

Available at:

<http://archive-ouverte.unige.ch/unige:155249>

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Hard Palate Melanoma: A Population-based Analysis of Epidemiology and Survival Outcomes

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Abstract. *Background/Aim:* Hard palate melanoma is an extremely rare and aggressive tumor arising from the mucosal epithelium of the oral cavity. The aim of this study was to analyze epidemiology, loco-regional treatment patterns and survival outcomes of this disease. *Materials and Methods:* The National Cancer Institute's Surveillance Epidemiology and End Results (SEER) database was searched for all cases of hard palate melanoma diagnosed between 1973 and 2012. The Kaplan–Meier method was used to calculate overall survival rate, log-rank test to compare survivals of different subgroups, and Cox hazard regression analysis to determine independent predictors of overall survival. *Results:* Overall, 83 patients were identified, 49 female and 34 males. The distribution among ages was: 13.3% <50 years, 38.6% between 50 and 69 years, 48.2% ≥70. Surgery alone was applied in 48.2% of patients, radiation therapy alone in 6%, and combination of surgery and radiation therapy in 33.7%. Overall 5-year survival was 26.3%. Survival with adjuvant radiation therapy was not longer than with surgery alone. *Conclusion:*

Hard palate melanoma is a rare malignancy mostly affecting the elderly, with low overall survival. The main treatment is surgical resection, while adjuvant radiotherapy does not improve survival. The establishment of an international registry is warranted to better define treatment options.

Primary oral melanoma is known to be an extremely rare and aggressive tumor arising from the mucosal epithelium of the oral cavity (1-5). The etiology and pathogenesis are poorly understood and, in contrast to the squamous cell oral carcinoma, no intraoral risk factors have been recognized to date (1-5). Incidence rates are not clearly identified in the literature but primary oral melanomas are reported to account for 0.2-8% of all melanomas in Europe and in the United States (6-8). Reports are mainly based on isolate or relatively small series of cases (2, 5-11).

The unusual primary site and the lack of early warning symptoms explain the advanced presenting stage of this tumor and the poor prognosis. The overall 5-year survival of primary oral mucosal melanoma is reported to be 15% (7). In early series that used mostly surgery alone the 5-year disease-specific survival rate of head and neck mucosal melanoma varied from 4.5-27% (12). The majority of mucosal oral melanoma occur in the hard palate (13), and even if the high frequency of this location has been confirmed by recent literature reviews and case series (14, 15), to date there is no clinical and histopathological explanation for this specific tumor site predilection.

Surprisingly, the epidemiological characteristics in terms of disease presentation and survival of this tumor subtype specifically occurring in the hard palate have never been studied in a comprehensive manner.

Our main goal was to analyze epidemiological and loco-regional treatment patterns and survival outcomes of primary

This work has been presented at the 5th European Association of Plastic Surgeons (EURAPS) Research Council - Joint Meeting with the 8th European Plastic Surgery Research Council (EPSRC), in Brussels, Belgium, May 25th through 26th, 2016.

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Key Words: Head and neck cancer, oral cancer, hard palate, mucosal melanoma, metastasis, treatment, prognostic factors, survival rates, SEER.

oral melanoma occurring in the hard palate in the United States, between 1973 and 2012, using the Surveillance, Epidemiology, and End Results (SEER) population-based registry of the National Cancer Institute. The SEER program is recognized as the most authoritative source of information on cancer incidence and survival in the United States (16). Data are updated annually, undergo vigorous quality control and are available to the public for research purposes.

Materials and Methods

A cohort of patients derived from the National Cancer Institute SEER database was analyzed. The study included 18 cancer registries as released on November 2014, which cover approximately 28% of the total US population based on the 2010 census (17). All patient data were de-identified hence there was no need for approval by an institutional review board.

Only cases of invasive primary hard palate melanoma diagnosed between 1973 and 2012 were included in the study. Eligible cases were identified using the codes of the International Classification of Oncology (ICD-O-3/WHO 2008) for tumor morphology (melanoma=8720-8790) and topographic location in the hard palate (C05.0-hard palate).

Using the “case-listing” option, demographic (age at diagnosis, race, marital status and year and geographic area of residency at diagnosis) and clinicopathological (historic stage, histological subtype, details of cancer-specific treatment, and survival in months) information were extracted for each case. SEER has standardized and simplified staging to ensure consistent definitions over time, defined as follows: localized cancer, when the disease is limited to the organ in which it began, without evidence of spread; regional cancer, when the disease has spread beyond the primary site to nearby lymph nodes or organs and tissues; distant cancer, when the disease has spread from the primary site to distant organs or distant lymph nodes; unstaged cancer, for those cases without enough information to indicate a stage.

The patients were categorized according to the geographic area of residence within the United States at the time of diagnosis: central (Detroit, Iowa, Kentucky, Louisiana, and Utah), eastern (Connecticut, New Jersey, Atlanta, rural Georgia) and western (Alaska, California, Hawaii, Los Angeles, New Mexico, San Francisco, San Jose, and Seattle).

In our cohort overall survival rate was determined using the Kaplan–Meier method. Subjects were assumed alive at the time of study cut-off (December 31st, 2012). In the SEER database, survival is calculated as the number of months between the date of cancer diagnosis and the date of death. The log-rank test was employed in order to compare overall survival between different subgroups. In addition, a Cox hazard regression analysis was performed in an attempt to determine independent predictors of overall survival.

Statistical analysis was performed with SPSS version 22 statistical package. Statistical significance was set at 0.05 for alpha level and all *p*-values were two-sided.

Results

A total of 83 cases of hard palate melanoma diagnosed between 1973 and 2012 were identified. The majority of

Table I. Demographic and clinicopathological characteristics of HPM patients.

	n (%)
Age at diagnosis	
<50	11 (13.3)
50-69	32 (38.6)
≥70	40 (48.2)
Race	
White	60 (72.3)
Black	7 (8.4)
Other	16 (19.3)
Gender	
Male	34 (41.0)
Female	49 (59.0)
Marital status	
Married	41 (49.4)
Unmarried	35 (42.2)
Unknown	7 (8.4)
SEER Registry	
Western	45 (54.2)
Eastern	17 (20.5)
Central	21 (25.3)
Year of diagnosis	
1973-1982	9 (10.8)
1983-1992	11 (13.3)
1993-2002	16 (19.3)
2003-2012	47 (56.6)
Stage	
Localized	37 (44.6)
Regional	27 (32.5)
Distant	11 (13.3)
Unstaged	8 (9.6)
Treatment	
No surgery or radiation	10 (12.0)
Surgery only	40 (48.2)
Surgery and Radiation	28 (33.7)
Only radiation	5 (6.0)
Reason for no surgery	
Not recommended	12 (14.5)
Recommended but not performed, patient refused	2 (2.4)
Recommended but not performed, unknown reason	1 (1.2)
Diagnosis	
8720/3: Malignant melanoma, NOS	52 (62.7)
8746/3: Mucosal lentiginous melanoma	7 (8.4)
8721/3: Nodular melanoma	5 (6.0)
8772/3: Spindle cell melanoma, NOS	5 (6.0)
8743/3: Superficial spreading melanoma	4 (4.8)
8730/3: Amelanotic melanoma	3 (3.6)
8744/3: Acral lentiginous melanoma, malignant	3 (3.6)
8742/3: Lentigo malignant melanoma	1 (1.2)
8745/3: Desmoplastic melanoma, malignant	1 (1.2)
8770/3: Mixed epithelioid and spindle cell melanoma	1 (1.2)
8771/3: Epithelioid cell melanoma	1 (1.2)

these cases (n=47, 56.6%) were diagnosed between 2003 and 2012. The general demographic and clinicopathological characteristics of our cohort are listed in Table I.

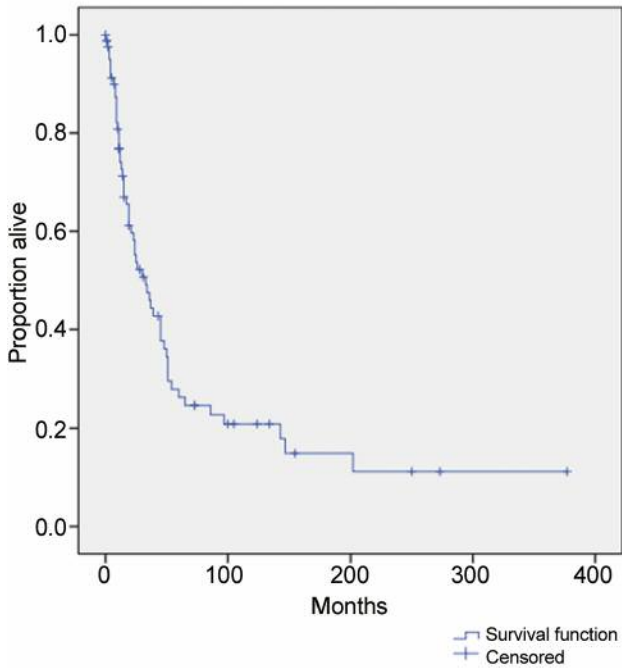


Figure 1. Kaplan–Meier analysis: overall observed survival.

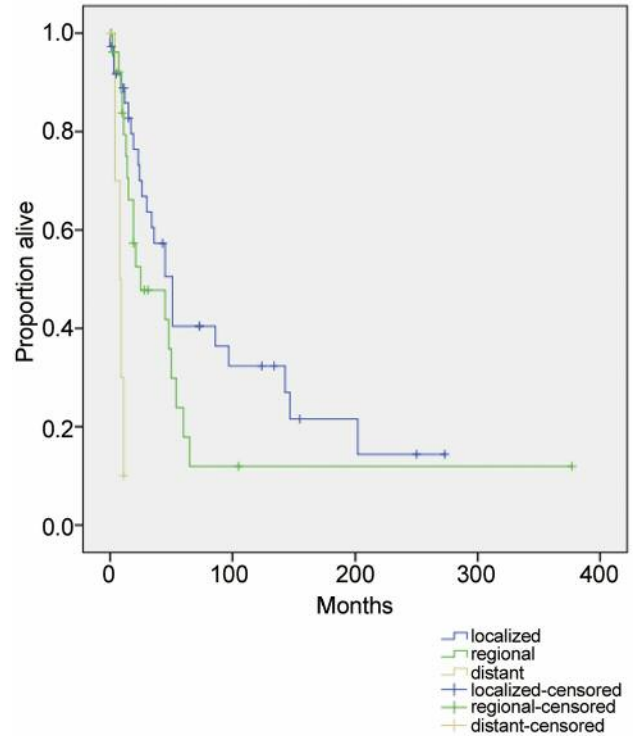


Figure 3. Kaplan–Meier analysis: observed survival of patients with hard palate melanoma stratified by stage.

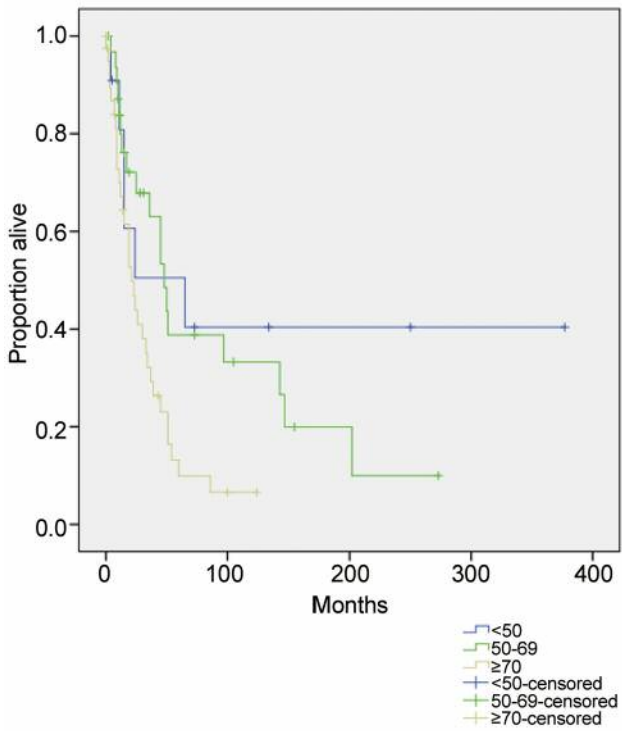


Figure 2. Kaplan–Meier analysis: observed survival of patients with hard palate melanoma stratified by age.

The age at diagnosis ranged between 26 and 87 years with a mean of 66, distributed among the study population as follows: 13.3% <50 years, 38.6% 50-69 years, 48.2% >70 years. Males represented 41% of the cases and females 59%. The cohort included 60 white patients (72.3%), 7 black patients (8.4%), and 16 patients (19.3%) classified as “other” (including American Indian/Alaska Native and Asian/Pacific Islander), with a white/black ratio of 8.6:1.

The most frequent histology was malignant melanomas (8720/3), that occurred in 52 patients (62.7%), followed by mucosal lentiginous melanoma (n=7, 8.4%). Patients presented with the following stages at diagnosis: localized in 44.6%, regional in 32.5%, distant in 13.3%, unstaged in 9.6%. Surgery alone was performed in 40 patients (48.2%), recommended but not performed in 2 patients (2.4%) and not performed and not recommended in 12 patients (14.2%). Radiation therapy alone was performed in 5 cases (6%). The combination of surgery and radiation therapy was performed in 28 patients (33.7%). In total, surgery was performed in 81.9% of patients, and when it was not performed the reasons were: not recommended (14.5%), recommended but not performed due to patient refusal (2.4%), and recommended, but not performed for unknown reason (1.2%).

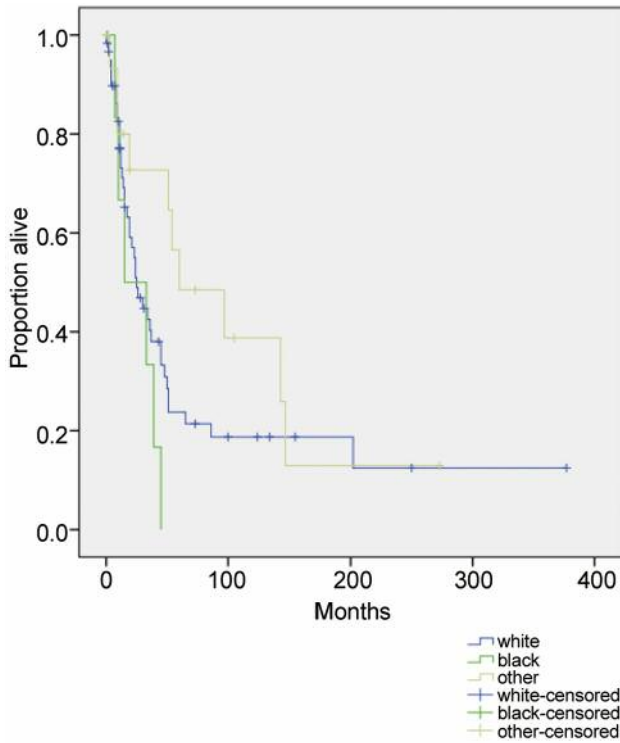


Figure 4. Kaplan–Meier analysis: observed survival of patients with hard palate melanoma stratified by race.

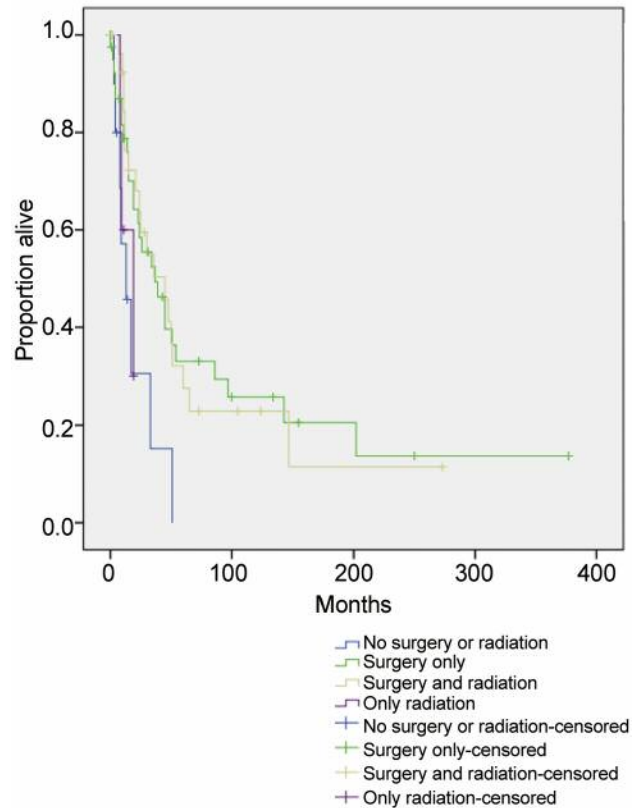


Figure 5. Kaplan–Meier analysis: observed survival of patients with hard palate melanoma stratified by treatment.

There was a linear direct increase in incidence along the decades: 10.8% of diagnoses were made during the decade 1973-1982, 13.3% during the decade 1983-1992, 19.3% during the decade 1993-2002, and 56.6% during the decade 2003-2012.

Survival analysis (Figure 1) revealed that overall 5-year survival rate in patients with hard palate melanoma was 26.3% (74% at 1 year, 59% at 2 year, 45.9% at 3 year, 36.2% at 4 year). Patients with an age below 50 years had a median survival of 65 months (95%CI=0-140.4), for patients between 50 and 69 it was 48 months (95%CI=33.3-62.7), and 21 months (95%CI=12.5-29.5) for patients of age equal or over 70 years (Figure 2). Survival of patients aged between 50 and 69 years was significantly higher than that of patients aged equal or over 70 (log-rank, $p=0.006$), while the higher survival of patients below 50 was not found to be significant (log-rank, $p=0.053$).

Median survival of patients with localized disease was 51 months (95%CI=35.6-66.4), 25 months for patients with regional disease (95%CI=0-59.7), and 8 months for patients with distant disease (95%CI=4.1-11.9), as shown in Figure 3. The advantage in terms of survival observed in patients with localized or regional disease in comparison with

patients with distant disease was statistically significant (log-rank, $p<0.001$). Instead, the difference in terms of survival between patients with regional and localized disease was not statistically significant (log-rank, $p>0.05$).

Regarding differences among racial groups, Kaplan–Meier survival analysis revealed a median survival equal to 25 months (95%CI=15.7-34.3) for white patients, 15 months (95%CI=0-42.6) for black, and 60 months (95%CI=0-125.5) for other (Figure 4). Survival of black patients was significantly lower than that of other (log rank, $p=0.007$).

With reference to different treatment options (Figure 5), a median survival of 13 months (95%CI=3.2-22.8) was observed for patients not receiving surgery or radiation, 37 months (95%CI=17-57) for patients undergoing surgery only, 45 months (95%CI=19.6-70.4) in cases of surgery and radiation, and 19 months (95%CI=3.4-34.6) in cases of radiation only. The group receiving no surgery or radiation had a significantly lower survival than the groups receiving surgery only (log-rank, $p=0.019$) or surgery and radiation (log-rank, $p=0.015$), while the difference was not significant in comparison with the group receiving radiation only (log-rank, $p=0.72$). There were no other differences statistically significant for the following comparisons: patients

undergoing surgery only *versus* patients undergoing surgery and radiation (log-rank, $p=0.96$), patients undergoing surgery only *versus* patients undergoing radiation only (log-rank, $p=0.237$), patients undergoing surgery and radiation *versus* patients undergoing radiation only (log-rank, $p=0.071$).

Cox regression multivariate analysis (Table II) revealed that independent predictors of cancer-specific survival (poorer prognosis) were stage with distant disease, white race, and age over 70. Although not statistically significant, surgery only and radiation only were close to confere an advantage in comparison to the combination of surgery and radiation (log-rank, $p=0.053$).

Discussion

Primary mucosal melanomas are extremely rare and biologically aggressive malignancies involving several anatomic districts: the head and neck (55.4% of the cases), the female genital tract (18%), the anal/rectal tract (23.8%), and the urinary tract (2.8%) (18). Overall, this variant of melanoma represents about 1.4% of all melanomas, in opposition to the cutaneous form which is estimated to be the fifth most common cancer in the United States among men, and the sixth among women (19-21). Previous reports have also indicated that incidence of mucosal melanoma is believed to remain stable while the incidence of cutaneous melanoma is growing (19, 22, 23). However, our research found a linear increase in the incidence of hard palate melanoma along the decades, with a peak in the decade 2003-2012.

With reference to the oral cavity, mucosal melanoma represents 1-2% of all malignancies, and is predominantly localized in the hard palate and maxillary alveolus (13, 24). In addition, the pathogenesis remains unclear, with mechanical trauma including injury from ill-fitting prostheses, infection, and tobacco use cited as possible causative factors (24, 25).

Importantly, increased expression of bcl-2, p53 and loss of p16 expression were reported as frequent and early events in the mucosal melanoma of the oral cavity, indicating that dysregulation of the G₁/S phase and impairment of programmed cell death may play a pathogenic role (24, 26).

Our research investigated epidemiology and survival outcomes of the mucosal melanoma localized in the hard palate. Indeed, despite its relevance in the context of oral mucosal melanomas, previous data are limited to several small single-institutional series or case reports, or are only partially included in papers that used a large US cohort to perform a global analysis of mucosal melanomas of the head and neck without a specific focus in this anatomical site (27, 28).

To this end, we used the SEER Program registries that collect data on patient demographics, primary tumor site, tumor morphology, stage at diagnosis, first course of treatment, and follow-up for vital status (16). The SEER Program is the most authoritative and comprehensive source

Table II. Multivariate Cox regression analysis for predictors of cancer-specific survival.

	B	Sig.	Exp (B)	95%CI for Exp(B)	
				Lower	Upper
Stage					
Localized		0.000			
Regional	0.472	0.251	1.604	0.717	3.589
Distant	2.963	0.000	19.365	5.316	70.542
Unstaged	-0.484	0.424	0.616	0.188	2.021
Race					
White		0.010			
Black	0.809	0.184	2.246	0.680	7.420
Other	-1.072	0.019	0.342	0.139	0.840
Year of diagnosis					
1973-1982		0.302			
1983-1992	-0.445	0.454	0.641	0.200	2.053
1993-2002	-1.092	0.081	0.336	0.099	1.143
2003-2012	-0.385	0.455	0.680	0.248	1.868
Marital status					
Married		0.267			
Unmarried	0.591	0.141	1.806	0.822	3.968
Unknown	0.581	0.295	1.788	0.603	5.306
Age at diagnosis					
<50		0.003			
50-69	0.401	0.470	1.493	0.503	4.428
≥70	1.451	0.007	4.269	1.479	12.326
Treatment					
No surgery or radiation		0.053			
Surgery only	-1.458	0.018	0.233	0.070	0.777
Surgery and Radiation	-0.840	0.154	0.432	0.136	1.371
Only radiation	-1.670	0.045	0.188	0.037	0.960

Bold prints, $p<0.05$.

of information on cancer incidence and survival, covering approximately one third of the US population (16).

Outcomes of 83 patients from the SEER Program were analyzed. The mean age of our study population was 66 years. Although there was a wide range from 26 to 87 years, only 13.3% of patients presented age at diagnosis below 50 and 48.2% was over 70, consistent with previous reports showing that this disease affects adults of all ages but is most common in the elderly population (13, 27, 29, 30). We found a female preponderance, in line with previous researches (7, 31), but in contrast with others who found male preponderance or no difference in the incidence of this tumor (28, 32-34). According to previous research, we also found a relatively higher incidence in the ethnic group designated as “others”, which also included Asians (7, 10, 24, 35, 36). Interestingly, white race was an independent adverse prognostic factor for survival. The overall survival at 5 years in our SEER cohort was 26.3%, consistent with the rate of 25.2% reported by a previous population-based analysis that included all mucosal melanomas of the head and neck (27).

Previous investigations have highlighted the importance of an early-stage diagnosis. Our research further supports these indications as it shows a significantly better survival for patients diagnosed with a localized or regional disease in comparison with distant disease. Cox regression multivariate analysis also indicated that the stage with distant disease is an independent predictor of lower cancer-specific survival. Delays in the diagnosis can be caused by the limited accessibility of the lesion with a dermoscope (24). Moreover, it was observed that approximately one third of oral melanomas are amelanotic, although in our cohort this subtype represented only 3.6% of all diagnoses (18, 37). However, according to our data, dermatologists are urged to be aware of the risk of hard palate melanoma and oral mucosal melanoma in general and include inspection of the oral cavity in regular melanoma check-ups (18, 24, 27).

With reference to the different treatment options, the general consensus is to perform complete surgical excision of the primary site, followed by postoperative radiation therapy to treat microscopic or macroscopic residual disease or nodal involvement (18). This is in line with what was observed in our cohort, where surgery alone or the combination of surgery and radiation therapy ensured a significantly better survival than no treatment. Instead, treatment including radiation therapy alone did not confer a significant improvement, confirming that this tumor shows unresponsiveness to conventional radiation therapy because of a high capacity for sublethal damage repair (18, 38).

Finally, according to Cox regression multivariate analysis, age over 70 was an independent predictor of poorer survival in our SEER cohort. This confirmed previous data reported by Jethanamest *et al.* (27), who also indicated age over 70 as predictor of worst survival, and partially confirmed the data reported by Sun *et al.* (33), who instead indicated an age over 55 as a cut-off. Conversely, our findings are in contrast with those reported by Wushou *et al.*, who indicated an age of 60 years or younger as an independent adverse prognostic factor for overall survival (14).

Conclusion

This population-based analysis has reported epidemiology and survival outcomes of patients with hard palate melanoma in the largest cohort systematically examined to date. The 5-year overall survival, equal to 26.3%, confirmed that the prognosis for this disease remains poor. Stage, age and race were identified as independent predictors of cancer-specific survival. Best treatment options were confirmed to be surgery or the combination of surgery and radiation therapy. However, the establishment of an international registry will be helpful in better defining treatment options.

Conflicts of Interest

The Authors have no conflicts of interest to disclose.

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Received August 23, 2018
Revised September 5, 2018
Accepted September 6, 2018